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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,519	09/09/2003	David Sidransky	JHU1300-6	6054

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Lisa A. Haile, J.D., Ph.D.
GRAY CARY WARE & FREIDENRICH LLP
Suite 1100
4365 Executive Drive
San Diego, CA 92121-2133

EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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10/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/659,519	**Applicant(s)** SIDRANSKY ET AL.	
	Examiner KATHERINE SALMON	**Art Unit** 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 September 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *12,15 and 19*.
   Claim(s) withdrawn from consideration: *20-24*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheet .
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Sarae Bausch/
Primary Examiner, Art Unit 1634

Continuation of 3A: NOTE: The proposed amendments to the claims will not be entered as the proposed amendments would raise new issues for consideration. Specifically the proposed amendments to Claim 12 would raise new issues under 35 USC 112/2nd paragraph.

Continuation of 11: NOTE: The reply traverses the 35 USC 112/enablement which is on record. The reply presents a summary of the amendments to the claims and points to particular passages in the specification to show support (p. 5). A summary of the arguments presented in the reply is provided below with response to arguments following.

(A) The reply traverses the conclusions in the previous office action (p. 5 5/21/2009) and asserts that the examiner's conclusion fails to consider the basis of the present invention which is that the exon 1 coding region can be lost via alternative splicing of p16 gene transcripts (p. 6 1st paragraph).

This argument has been fully reviewed but has not been found persuasive.

The claims are drawn to a correlation of the presence of the truncated p16 gene product with a homozygous deletion of exon 1 with lung or head and neck cancer. The claims are not drawn to detection of the exon 1 coding region which can be lost via alternative splicing of p16 gene transcript, but to the correlation of the homozygous deletion to lung or head and neck cancer. As stated in the last office action (5/21/2009) the instant specification has not provided such support that in any sample there is correlation weighed against the art which teaches that such correlations are unpredictable.

(B) The reply asserts that that although the examiner cites Zhang et al. which teaches that none of the primary head and neck squamous cell carcinomas homozygous deletions of p16, that the invention shows that the methods used in Zhang may contribute to an underestimation of inactivation of p16 in tissue samples (p. 6 last paragraph).

This argument has been fully reviewed but has not been found persuasive.

The reply points to the specification on pages 74 to 75 to support that the invention used by Zhang et al. may contribute to an underestimation of inactivation of p16. The specification at these cited pages assert that consistent observations of homozygous deletion of p16 in primary tumors are difficult to detect by contamination by normal cells. The specification asserts that detection of aberrant DNA methylation of the p16 gene is not limited by the problem. However, the claims are towards contacting a sample comprising RNA and detecting the presence of a truncated p16 gene product. The claims are not limited to detection of methylation. Zhang et al. teaches that none of the head and neck squamous cell carcinomas showed homozygous deletions of p16 (abstract). Zhang et al. further teaches that although p16 may play a role in tumorigenesis in some head and neck squamous cell carcinomas, it probably occurs more frequently in cell lines as a result of adaptation to cell culture. Therefore the passages pointed out by the reply are drawn to methylation steps which are not present in the instant claim set and therefore do not overcome the unpredictably shown by Zhang et al. towards detection of homozygous deletions of p16.

(C) The reply asserts that although the examiner cites Okamoto et al. as supporting the assertion of a lack of correlation between homozygous deletion of p16 and lung cancer, the applicant note that the present inventor cites Okamoto as supporting the importance of p16 abnormalities in lung cancer (p. 7 1st and 2nd paragraph).

This argument has been fully reviewed but has not been found persuasive.

The cited passage of the instant specification asserts that in brain tumors and lung carcinomas, the later stage tumors have been reported to have higher rates of homozygous deletion of p16 suggested that p16 abnormalities may be a late progression event. This cited passage goes towards the support of the enablement, because the instant specification discloses that homozygous deletions of p16 might be only observable in late stage lung cancer. Further the cited reference states that p16 deletion is a late event in NSCLC carcinogenesis and that there is no association in other types of lung cancers (abstract). As such Okamoto et al. shows that there is not correlation between deletion of exon 1 and lung cancer.

(D) The reply asserts that none of these references disclose or suggest a 5'ALT alternative transcript of p16 as a means of inactivating p16 (p. 7 2nd paragraph). The reply asserts that thus the correlations that the authors cited may or may not have found are not relevant to the instant method of detecting a cell proliferative disorder by detecting the presence of a 5'ALT alternative p16 transcript devoid of the p16 exon 1 coding sequence (p. 7 2nd paragraph).

This argument has been fully reviewed but has not been found persuasive.

The claims are drawn to a correlation of the presence of the truncated p16 gene product with a homozygous deletion of exon 1 with lung or head and neck cancer. The claims are not drawn to only inactivating p16 gene by 5'ALT alternative transcript of p16. The cited references of Zhang, Washimi et al, and Okamoto et al., clearly teach that correlations of the homozygous deletion of p16 and lung and head and neck cancer are dependent on the sample detected. The art discloses that associations observed in cell lines are different than those observed in tumor samples (Zhang et al.). Further as pointed out by the instant specification Okamoto teaches that these alterations are found only in lave event NSCLC carcinogenesis. As such the art discloses the unpredictably in the art with regard to the association of the deletion of a region of the p16 gene and lung or head and neck cancer.

(E) The reply asserts that the specification provides a correlation between p16 methylation and 5'ALT alternative p16 transcripts and cancer (p. 7 last paragraph). The reply points to example 6 asserting that the methylation status of the 5'CpG island of the p16 gene in a number of cancer cell lines (p. 7 last paragraph). The reply asserts that the 5'CpG island of the p16 gene is fully methylated in a number of cancer cell lines and primary cancers, but is unmethylated in all normal tissues (p. 7 last paragraph). The reply asserts that the specification provides RTPCR of total RNA in 8 tumor cell limes (without homozygous deletion) confirmed the presence of both alternative transcripts (p15ALT and p16ALT) (p. 7 last paragraph).

This argument has been fully reviewed but has not been found persuasive.

The reply points to example 6 in the instant specification for support for the correlation of the deletion of a region of the p16 gene and lung or head and neck cancer. It is noted that Example 6 is drawn to methylation status, as discussed above; the claims are not limited to methylation status.

The instant specification on p. 56-57 (as cited in the reply) states "RTPCR of total RNA from eight tumor cell lines (without homozygous deletion of this region) confirmed the presence of both alternative transcripts (p15ALT and p16ALT)". This citation from the specification does not support the enablement of the claims because as discussed on p. 5-6 of the last office action the instant specification provides conflicting assertions of these associations. As discussed on p. 5 of the last office action the specification asserts that the p16 sequence indicates the majority of the primary human cancers, including head and neck and lung cancer have the wild-type p16 sequence (p. 61). As such these cancers would not have the homozygous mutant p16 gene. Further, the art, as discussed above, teaches that these associations are sample specific. The art teaches that associations in cell lines are not correlative to tumors (see Zhang et al.). The art teaches that associated observed in late event NSCLC are not observed in early stages (see Okamoto et al.). Therefore the 35 USC 112/Enablemeent made in the last office action is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-530PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon